

Appendix 4
ALPHAGAN Canadian
Package Insert

ALPHAGAN®

Brimonidine Tartrate 0.2% Ophthalmic Solution ELEVATED INTRACULAR PRESSURE THHERAPY

STERILE

ACTIONS AND CLINICAL PHARMACOLOGY: Mechanism of Action: Brimonidine tartrate is a relatively selective alpha adrenergic receptor agonist that in radioligand binding assays and in functional assays, is approximately 1000 times more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoceptor. This selectivity results in the absence of vasoconstriction in microvessels associated with human retinal xenografts. Topical administration of brimonidine decreases intraocular pressure (IOP) in humans. When used as directed, ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2% reduces elevated IOP with minimal effect on cardiovascular parameters.

ALPHAGAN® has a rapid onset of action, with the peak ocular hypotensive effect occurring at approximately two hours post-dosing. The duration of effect is 12 hours or greater.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. ALPHAGAN® lowers IOP by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacodynamics: ALPHAGAN® 0.2% has no effect on pulmonary function or exercise-induced tachycardia. The cardiovascular effects of ALPHAGAN® 0.2% during exercise in normal volunteers were found to be limited to a slight suppression of systolic blood pressure which was clinically insignificant, during the 200 m run test, following a treadmill test.

Pharmacokinetics: After oral, intramuscular, or topical application of ALPHAGAN® 0.2% twice daily (both eyes) in humans for 10 days, plasma concentrations were $\text{C}_{\text{max}} = 0.06 \text{ ng/mL}$. Plasma brimonidine levels peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours.

In humans, brimonidine is eliminated rapidly via extensive systemic metabolism; there is no marked metabolic accumulation after multiple dosing. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 8% of an orally-administered radioactive dose was eliminated within 12 hours with 74% found in the urine in the first 96 hours.

Clinical Studies: ALPHAGAN® 0.2% lowers intraocular pressure with minimal effect on cardiovascular parameters (heart rate, systolic and diastolic blood pressure) and no apparent effect on pulmonary parameters (spirometry, respiratory rate).

The long term efficacy of ALPHAGAN® 0.2% dosed b.i.d. was demonstrated in two one-year multicentre studies in subjects with open angle glaucoma or ocular hypertension. In these trials ALPHAGAN® 0.2% lowered IOP by mean values of 4.3 mmHg at trough and 6.7 mmHg at peak. IOP decreases were maintained for the duration of the studies in the majority of patients; no achlyphaxis was observed. Nine percent of subjects were discontinued from the studies due to inadequately controlled intraocular pressure.

INDICATIONS AND CLINICAL USE: ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2% is indicated for the control of intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS: ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2% is contraindicated in patients with hypersensitivity to brimonidine tartrate or an component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

WARNINGS: FOR TOPICAL OPHTHALMIC (USE ONLY).

The use of ALPHAGAN® in paediatric patients is currently not recommended. Several serious adverse reactions have been reported in association with the administration of ALPHAGAN® (brimonidine tartrate) Ophthalmic Solution 0.2% to infants in the age range of 28 days to 3 months (See Adverse Reaction sections).

PRECAUTIONS: General: ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2% should be used with caution in patients with known hypersensitivity to other alpha-adrenoceptor agonists. Although ALPHAGAN® had minimal effect on blood pressure and heart rate of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease. ALPHAGAN® has not been studied in patients with hepatic or renal impairment; caution should be exercised in treating such patients. ALPHAGAN® should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

Drug Interactions: Although specific drug interaction studies have not been conducted with ALPHAGAN®, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or analgesics) should be considered.

ALPHAGAN® 0.2% did not have hemodynamically significant effects on pulse and blood pressure in chronic clinical studies. However, since alpha-agonists act as a class, may reduce pulse and blood pressure, caution in the concomitant use of drugs such as beta-blockers (ophthalmic and/or systemic), antihypertensives and/or cardiac glycosides is advised. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with ALPHAGAN® can lead to an interference in IOP lowering effect. No data are available on the level of circulating catecholamines after ALPHAGAN® is instilled. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No compound-related carcinogenic effects were observed in 21 month and 2 year studies in mice and rats given oral doses of 2.5 mg base/kg/day and 1.0 mg base/kg/day, respectively. These oral doses are approximately 230 and 330 times greater, respectively, than the maximum recommended human daily ophthalmic dosage to ALPHAGAN® 0.2% (0.003 mg base/kg/day), based on a 60 kg human.

Brimonidine was not mutagenic or cytogenetic in a series of *in vitro* and *in vivo* studies including the Ames test, host-mediated assay, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, cytogenetic studies in mice and dominant lethal assay.

Use in Pregnancy: Teratogenicity studies showed no adverse effects in rats and rabbits when oral doses (1.65 mg base/kg/day and 3.33 mg base/kg/day) were administered at approximately 550 and 1110 times, respectively, the maximum recommended human daily ophthalmic dosage for ALPHAGAN® 0.2%, based on a 60 kg human. There are no studies of ALPHAGAN® in pregnant women, however in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent (ratio of drug-related material in fetal/maternal blood = 0.1 - 0.3). Drug-derived material was eliminated from fetal tissues by 24 hours post-dose. ALPHAGAN® should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether brimonidine is excreted in human milk, although in animal studies brimonidine has been shown to be excreted in breast milk. During treatment with ALPHAGAN® 0.2%, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in Pediatrics: The use of ALPHAGAN® in paediatric patients is currently not recommended. Several serious adverse reactions have been reported in association with the administration of ALPHAGAN® (brimonidine tartrate) Ophthalmic Solution 0.2% to infants in the age range of 28 days to 3 months (See Adverse Reaction sections).

Information to be Provided to the Patient by the Physician: ALPHAGAN®, as with other similar medications, can potentially cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

The preservative in ALPHAGAN® 0.2% benzalkonium chloride may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling ALPHAGAN® to insert soft contact lenses.

ADVERSE REACTIONS: In clinical studies including 717 patients on ALPHAGAN® 0.2%, the most frequently reported adverse events were oral dryness [25.8%], ocular hyperemia [24.8%], burning and stinging [22.5%], blurring [17.3%], headache [16.3%], foreign body sensation [15.5%], fatigue/drowsiness [15.2%], tearing/staining/irritation [10.0%], ocular allergic reactions [9.9%], and ocular pruritis [9.8%], and conjunctival follicles [9.6%].

Events occurring less frequently included photophobia [7.4%], ocular dryness [7.0%], eyelid erythema [6.1%], ocular asthenia [6.0%], upper respiratory symptoms [6.0%], tearing [5.6%], conjunctival edema [5.3%], eyelid edema [4.9%], dizziness [4.2%], conjunctival blanching [3.8%], blepharitis [3.6%], ocular irritation [3.1%], gastrointestinal symptoms [3.1%], asthenia [2.8%], abnormal vision [2.6%], abnormal taste [1.4%], conjunctival discharge [1.4%], conjunctival papilla [1.0%], and nasal dryness [1.0%]. The following adverse reactions were reported infrequently (<1%): depression [0.6%], systemic allergic reactions [0.5%], and palpitations [0.4%].

Serious Reports of Adverse Reactions in Paediatric Patients: Several serious adverse reactions have been reported in association with the administration of ALPHAGAN® (brimonidine tartrate) Ophthalmic Solution 0.2% to infants in the age range of 28 days to 3 months. These reactions included bradycardia, hypotension, hypothermia, hypotonia, apnea, dyspnea, hyperventilation, cyanosis and tetany, resulting in hospitalization. Upon discontinuation of ALPHAGAN® the infants recovered without sequelae.

SYMPOTMS AND TREATMENT OF OVERDOSE: No data are available on overdosage of ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2% in humans. Treatment of an oral overdose includes supportive and symptomatic therapy. A patent airway should be maintained. Evacuation of the stomach should be considered during the first few hours after an overdosage.

DOSAGE AND ADMINISTRATION: The recommended dose is one drop of ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2% in the affected eye(s) twice daily (doses taken approximately 12 hours apart). **COMPOSITION:** Each mL of ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2% contains brimonidine tartrate 0.2 mg with the following non-medical ingredients: 0.005% benzalkonium chloride as preservative, citric acid, polyvinyl alcohol, purified water, sodium chloride and sodium citrate. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

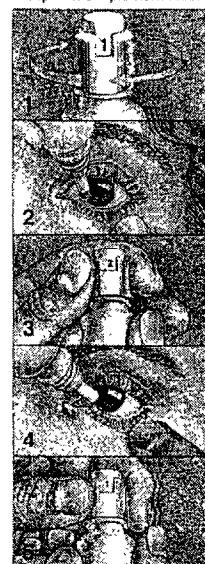
STORAGE: ALPHAGAN® 0.2% should be stored at 15°C to 25°C.

HOW SUPPLIED: ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2% is supplied in white opaque plastic dropper bottles; with C Cap® Compliance Cap b.i.d. (twice daily) containing 5 mL and 10 mL.

INFORMATION FOR THE CONSUMER

You can help preserve your vision by taking your glaucoma eye drops exactly as your doctor tells you. But sometimes it is hard to remember when to take your drops. That's why your doctor has prescribed these drops. They have a special cap called the C Cap®. It was designed to help you adhere to your eye drop schedule by "making it" easy to keep track of how many times you use your drops each day. For Allergan's various glaucoma products there are several different versions of the C Cap®. Your doctor has chosen the one that corresponds to the number of times you use your medicine each day.

C Cap® - A Simple Reminder



HOW TO USE THE C CAP®

1. The very first time you are ready to take your eye drops and at the beginning of each day, look in the window of the cap to make sure the number "1" appears. If another number is showing, turn the cap clockwise until it is in the correct position. You will notice that the cap "clicks" as it changes positions (See picture 1).
2. Next remove the C Cap® and apply your eye drops as directed by your doctor. For ALPHAGAN® 0.2% this means that the eye drops are given two times daily 12 hours apart (See picture 2).
3. Replace the cap by turning clockwise until it is snug. Then keep twisting the cap slowly until you hear the "click". The number "2" will appear in the window (See picture 3).
- This means for ALPHAGAN® 0.2% that the next time you take your eye drops it will be the second time for that day 12 hours after the first time.
4. When it is time for your next eye drops, unscrew the cap and apply your drops (See picture 4).
5. Replace the cap and click it to the next position. For ALPHAGAN® 0.2% this will be number "1" again, as the next time you take the drops will be at the beginning of the next day (See picture 5).

NOTE: If you forget to apply your eye drops at your normal time, simply apply them as soon as you remember. Then go back to the original schedules directed by your doctor. Don't try to catch on missed drops by applying more than one dose at a time.

REMEMBER: EACH TIME YOU REPLACE THE CAP YOU SHOULD KEEP TURNING UNTIL YOU HEAR THE CLICK.

Do not allow the dropper tip of the bottle to touch the eye or other surrounding structures, because this could contaminate the tip with common bacteria known to cause eye infections. Serious damage to the eye with subsequent loss of vision may result if you use eye drop solutions that have become contaminated. If you experience any type of eye condition or have surgery, immediately seek your doctor's advice concerning the continued use of the bottle you are using.

Patients Wearing Soft Contact Lenses: Lenses should be removed prior to application of ALPHAGAN® 0.2% and not re-inserted earlier than 15 minutes after use.

Product Monograph available on request.

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